

**FEDERAL BUREAU OF PRISONS  
CLINICAL PRACTICE GUIDELINES  
TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI)  
AND TUBERCULOSIS DISEASE  
FEBRUARY, 2001**

**PURPOSE**

The Federal Bureau of Prisons Clinical Practice Guidelines for Latent Tuberculosis Infection and Tuberculosis Disease provide recommendations for the medical management of federal inmates with *Mycobacterium tuberculosis* infection and disease.

**REFERENCES**

Targeted tuberculin testing and treatment of latent tuberculosis infection, American Thoracic Society/Centers for Disease Control and Prevention Statement, Committee on Latent Tuberculosis Infection, *MMWR*, 2000;49(No. RR-6):1-51, and *Am J Respir Crit Care Med*, 2000;161:S221-S247.

Diagnostic standards and classification of tuberculosis in adults and children, official statement of the American Thoracic Society and the Centers for Disease Control and Prevention, *Am J Respir Crit Care Med*, 2000;161:1376-1395.

Self-Study Modules on Tuberculosis: *Contact Investigations for Tuberculosis*, October 1999, Centers for Disease Control and Prevention.

Core Curriculum on Tuberculosis, *What the Clinician Should Know*, Fourth Edition, 2000, Centers for Disease Control and Prevention.

Prevention and control of tuberculosis in correctional facilities: Recommendations of the advisory council for the elimination of tuberculosis, *MMWR*, 1996;45(No. RR-8):1-27.

Guidelines for Preventing Transmission of *Mycobacterium tuberculosis* in Health-Care Facilities, *MMWR*, 1994;43:(No. RR-13):69-105.

Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: Principles of therapy and revised recommendations, *MMWR*, 1998;47(No. RR-20):1-58.

Drug-susceptible tuberculosis outbreak in a state correctional facility housing HIV-infected inmates - South Carolina, 1999-2000, *MMWR*, 2000;49(46):1041-1044.

Jones TF, Craig AS, Valway SE, Woodley CL, and Schaffner W., Transmission of tuberculosis in a jail, *Ann Intern Med*, 1999; 131:557-563.

Ending Neglect: The Elimination of Tuberculosis in the United States, Institute of Medicine, National Academy Press, Washington, DC, 2000.

Dye C, Scheele S, Dolin P, Pathaniz V, and Ravigliione M. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country, *JAMA*, 1999;282(7):677-686.

## **DEFINITIONS**

**Acid-fast bacilli (AFB)** are bacteria that retain certain dyes after being washed in an acid solution. Most acid-fast bacilli are mycobacteria. When AFB are seen on a stained smear of sputum or other clinical specimen, a diagnosis of TB should be suspected; however, the diagnosis of TB is not confirmed until a culture is grown and identified as *M. tuberculosis*.

**Airborne exposure** is the condition of being subjected to an infectious agent that could have a harmful effect if airborne transmission occurs. A person exposed to *M. tuberculosis* does not necessarily become infected.

**Airborne precautions** are protective measures used for patients/inmates and situations to prevent the spread of infections that can be transmitted by airborne contact with infectious agents that remain suspended in the air when indoors over a period of time. Precautions include the wearing of appropriate personal respiratory protection (i.e. high efficiency particulate air [HEPA] or N-95 mask) for persons who come in direct contact with infectious airspace, the isolation of infectious patients/inmates in a private room with monitored, negative air pressure, and the implementation of necessary engineering controls to inform, direct, and protect persons entering the isolation room.

**Anergy** is the inability of a person to react to skin test antigens (even if the person is infected with the organisms tested) because of immunosuppression.

**BCG** is Bacillus Calmette-Guerin: vaccinations used in many parts of the world to prevent TB.

**Booster phenomenon** occurs when persons (especially older adults) many years after initial infection with *M. tuberculosis* have a negative reaction to an initial skin test, followed by a positive reaction to a subsequent skin test. The second positive reaction is caused by a boosted immune response, indicating latent TB infection.

**Clearance time** is the time between the discharge of an inmate isolated for TB precautions in a negative pressure isolation room (NPIR) and the arrival of another inmate or other person(s) who will occupy the NPIR without the use of airborne precautions.

**Clinician** is a physician or mid-level provider.

**Contact** is a person who has shared the same air with a person who has infectious TB for a sufficient amount of time to allow possible transmission of *M. tuberculosis*.

**Culture** is the process of growing bacteria in the laboratory so that organisms can be identified.

**Delayed-type hypersensitivity (DTH) reaction** is a cellular immunologic response caused by lymphokines released from T cells that have been sensitized by prior infection with a specific antigen.

**Directly observed therapy (DOT)** of latent tuberculosis infection (LTBI) and TB disease is the unit dose administration of tuberculosis medications to an inmate by a clinician, nurse, pharmacist, or specially trained staff, under direct observation of ingestion.

**Drug susceptibility tests** are the laboratory tests that determine whether the TB bacteria cultured from a patient are susceptible or resistant to various anti-tuberculosis drugs.

**Index case** is the initial person who has suspected or confirmed infectious TB who may have been in contact with other persons while sharing the same air space for a sufficient amount of time to allow possible transmission of *M. tuberculosis*.

**Intradermal** is within the layers of skin.

**Latent tuberculosis infection (LTBI)** is a condition in which a

relatively small number of living tubercle bacilli (*M. tuberculosis*) are present in the body but are not multiplying or causing clinically active disease. Although persons with LTBI usually have positive tuberculin tests, they have no symptoms or other objective evidence of TB disease and are not infectious to others. Persons with LTBI, however, have a lifelong risk for developing active TB disease.

**Mantoux method** is the most reliable method of tuberculin skin testing, involving the intradermal injection of PPD-tuberculin into the forearm with a needle and syringe.

**Multi-drug resistant tuberculosis (MDR-TB)** is active TB caused by *M. tuberculosis* organisms that are resistant to more than one anti-tuberculosis drug; in practice, often refers to organisms that are resistant to both isoniazid and rifampin with or without resistance to other drugs.

***Mycobacterium tuberculosis*** is the mycobacterial species that is the primary cause of active TB disease in the United States.

**Negative Pressure Isolation Room (NPIR)** is a room designated for the isolation of patients with contagious TB disease that has adequate directional airflow, air exchanges, and exhaust that reduce transmission of *M. tuberculosis*, in accordance with Centers for Disease Control and Prevention guidelines.

**Personal respiratory protection** is the use of respirators to protect a person from the transmission of airborne infectious agents. Particulate respirators indicated for protection against *M. tuberculosis* are selected and worn based on recommendations from the Centers for Disease Control and Prevention and certification criteria from the National Institute for Occupational Safety and Health (NIOSH).

**Positive tuberculin skin test** is the induration measured in millimeters that develops after the intradermal injection of PPD-tuberculin, indicative of previous infection with *M. tuberculosis*. The extent of induration that determines a positive test depends on the medical history and risk factors of the person being tested in accordance with the following:

5 millimeters - positive for:

- Close contacts of an active case of TB
- Inmates with HIV infection, treatment for organ

transplantation, or other immunocompromised conditions, or inmates with HIV risk factors and unknown HIV serostatus

- Inmates with evidence of old tuberculosis infection by chest radiograph.

10 millimeters - positive for all other inmates and correctional staff

**Purified protein derivative (PPD)** tuberculin is the most common agent used for tuberculin skin testing to evaluate the likelihood that a person is infected with *M. tuberculosis*.

**Recent convertor** is an individual who has a negative tuberculin skin-test reaction that increases in reaction size by  $\geq 10$  millimeters (mm) within a period of two years, suggestive of recent infection with *M. tuberculosis*. (In persons who have been infected with nontuberculous mycobacteria or have received BCG vaccination, the skin test may show some degree of induration; and for these persons a conversion to a positive test is defined as an increase in induration by 10 millimeters on subsequent tests).

**Smear (AFB smear)** is the laboratory technique for visualizing mycobacteria. The specimen is smeared onto a slide and stained, then examined using a microscope. A large number of mycobacteria seen on an AFB smear from a person with TB usually indicates infectiousness. However, a positive smear is not diagnostic of TB, because acid-fast organisms other than *M. tuberculosis* may be seen on an AFB smear.

**Surgical mask** is a disposable paper type mask used to prevent respiratory secretions from the person wearing the mask from entering into the air. A surgical mask does not protect a person from transmission of airborne bacteria.

**Tuberculosis disease** is a clinically active disease caused by organisms of the *Mycobacterium tuberculosis complex*, which are sometimes referred to as tubercule bacilli. Symptoms of TB disease depend on the site of active disease. Pulmonary TB, the usual form of TB, is characterized by chronic cough, hemoptysis, and chest pain. General symptoms of TB include fever, chills, night sweats, easy fatigability, loss of appetite, and weight loss.

**Two-step testing** is baseline tuberculin testing that is repeated

if negative after a short time period to reduce the future likelihood of mistaking a boosted reaction for a new infection with *M. tuberculosis*. If the initial baseline tuberculin skin-test result is classified as negative, a second test is repeated several weeks later. If the reaction to the second test is positive, it represents a boosted reaction indicating old latent TB infection. If the second test result is also negative, the person is classified as not infected with *M. tuberculosis*.

## **PROCEDURES**

### **1. DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION (LTBI)**

The tuberculin skin test is the only proven method for diagnosing *M. tuberculosis* infection in persons who do not have TB disease. All available testing antigens are less than 100% sensitive and specific. The tuberculin skin test has a specificity of approximately 99% in populations that have no other mycobacterial exposures or BCG vaccination, but the specificity decreases where cross-reactivity with other mycobacteria is common. The general population of the United States has an estimated *M. tuberculosis* infection rate of 5 to 10%. Foreign born populations have an average estimated *M. tuberculosis* infection rate of 32%, however, rates of infection differ significantly throughout the world.

**Indications for tuberculin skin testing:** Inmates should be evaluated for TB infection with tuberculin skin testing in accordance with BOP policy and Centers for Disease Control (CDC) and Prevention Guidelines. Inmates with negative tuberculin skin tests should be tested for LTBI in accordance with Bureau policy and the following medical indications:

- Upon incarceration (tuberculin skin test documentation during the past year from local jails is acceptable for TB screening purposes, however, repeat tuberculin skin testing is recommended for inmates who have been transferred from local detention centers, particularly in regions of the country with high rates of TB). For BOP inmates who are transferred frequently to and from local jails, testing should be repeated as recommended by the evaluating clinician, but no more than quarterly.
- As part of annual screening.
- When medically indicated if active TB disease is clinically suspected.

- As part of a TB contact investigation.

All inmates tested for LTBI by tuberculin skin testing should also be interviewed for symptoms of TB disease: chronic cough, hemoptysis, fever, night sweats, and unexplained weight loss. By certain estimates, 25% of persons with active TB disease have a false-negative tuberculin skin test, therefore all inmates with symptoms of active TB should be referred to a physician for further diagnostic evaluation regardless of tuberculin skin test results.

#### **Administration of the tuberculin skin test:**

- The tuberculin skin test should be administered by the Mantoux method through the intradermal injection of 0.1 mg (0.1 ml) of purified protein derivative (PPD) tuberculin containing 5 tuberculin units (TU) into the volar or dorsal surface of the forearm, using a disposable tuberculin syringe. Other areas may be used, but the forearm is the preferred site for testing. A skin area away from superficial veins and free of lesions should be selected.

- The tuberculin solution should be injected just beneath the surface of the skin with the needle bevel upward. A discrete elevation of the skin or wheal (6 to 10 millimeters in diameter) should be produced. If the first test is improperly administered, a second test dose can be immediately administered at a site several centimeters from the initial test site.

- Only BOP Formulary tuberculin solution should be used. Tuberculin should never be transferred from one container to another to minimize reduction in potency by adsorption. Skin tests should be administered as soon as possible once the tuberculin syringe has been filled. The tuberculin test solution should be refrigerated (not frozen) and stored in the dark as much as possible (exposure to strong light should be avoided).

- The tuberculin skin test should be read by a trained health care worker 48 to 72 hours after injection. A positive reaction may be measurable up to one week after testing and is considered valid, however, readings after 72 hours tend to underestimate the true size of induration. A negative reaction read after 72 hours is invalid.

- The tuberculin reaction is quantified by measuring the largest diameter of the indurated area (palpable swelling) on the forearm in millimeters (mm). The diameter of the induration should be

measured transversely to the long axis of the forearm for standardization purposes. Erythema (redness) without induration is not significant. The tuberculin skin test results should always be documented in millimeters, not as positive or negative.

- A self-reported, "previously positive" skin test (without a millimeter reading) is not a contraindication to repeat testing unless a severe reaction has been documented or described by the inmate (e.g. entire arm swelling, blistering). Inmates with a positive documented tuberculin skin test measured in millimeters should not be repeatedly tested.

- Multi-puncture tests (Tine) are poorly standardized and should not be administered.

- Pregnancy is not a contraindication to tuberculin skin testing.

- Bacillus Calmette-Guerin (BCG) vaccination is not a contraindication to tuberculin skin testing. Tuberculin skin test reactivity resulting from BCG vaccination does not correlate with protection against TB. Since there is no reliable method for distinguishing tuberculin reactions caused by BCG from those caused by infection with *M. tuberculosis*, persons with a positive tuberculin skin test with a history of BCG vaccination should be considered infected with *M. tuberculosis*.

- Anergy testing is not medically indicated as a component of tuberculin skin testing for inmates. Anergy panel antigens are poorly standardized and the antigenic responses are not necessarily predictive of an adequate cellular immune response to PPD tuberculin.

- Two-step testing should be considered for the following newly sentenced inmates at high risk of boosting who have not received a tuberculin skin test in the past 12 months and for whom repeated annual testing is anticipated:

- Inmates over 50 years of age

- Foreign born inmates

- Inmates with a history of BCG vaccination

- Other inmates as medically indicated with suspected previous exposures to *M. tuberculosis*

## **2. BASELINE EVALUATION FOR TREATMENT OF LTBI**

Inmates with tuberculin skin tests of 5 millimeters of induration or greater should be referred for evaluation by a physician for possible treatment and to preclude the presence of active TB disease. The baseline evaluation for treatment of LTBI should include, but not necessarily be limited to the following:

- **Medical history** that includes: risk factors for TB, prior treatment for TB or LTBI, review of preexisting medical conditions that may complicate treatment, review of current medications with attention to potential drug interactions, and review of symptoms of active TB disease, hepatitis, liver disease, and pregnancy.
- **Targeted examination** by a clinician for systemic signs of active TB disease (e.g. fever, weight loss, pulmonary findings) and for signs of hepatitis.
- **Chest radiographs:** The treatment of LTBI should never be initiated until active TB disease has been eliminated as a potential diagnosis with a posterior-anterior chest radiograph and documented negative assessment for signs and symptoms of TB.
  - **X-rays in pregnancy:** Because of the risk of serious TB disease and/or congenital TB, pregnant women with a positive tuberculin skin test, OR who have negative skin test results but are recent contacts of persons with infectious TB disease, should have chest radiographs performed (with appropriate shielding) as soon as feasible, even during the first trimester of pregnancy.
- **Liver transaminases:** ALT (SGPT) or AST (SGOT) and other laboratory tests as clinically indicated. Although baseline liver transaminases are not routinely recommended prior to initiating LTBI treatment, screening is recommended for federal inmates, because of the high incidence of substance abuse and associated liver disease among incarcerated populations. If liver transaminases are elevated, liver function tests (e.g. bilirubin) should also be assessed.
- **HIV counseling and testing** if not done previously, since HIV co-infection significantly increases the risk of developing TB disease.
- Sputum examination is not routinely indicated for most persons being considered for LTBI treatment. Inmates with chest radiographs suggestive of old healed TB, however, should have **three** consecutive sputum samples, obtained on different days and

submitted for AFB smear and culture to rule out active TB disease. Inmates with HIV infection and respiratory symptoms or unexplained fever or weight loss, should also have sputums submitted for bacteriologic cultures, since active TB disease in immunocompromised hosts is often cryptic. If sputum smears and cultures are negative and the inmate's symptoms or radiographic findings can not otherwise be clinically explained, further diagnostic evaluations (e.g. bronchoscopy) for active TB disease should be pursued. During the diagnostic evaluation, empiric treatment for active TB disease can be considered on a case by case basis depending on the inmate's symptoms and radiographic findings. Single drug treatment of LTBI should never be instituted while an evaluation for active TB disease is being pursued.

### **3. INDICATIONS FOR TREATMENT OF LTBI**

Clinical indications for the treatment of LTBI are based on the inmate's tuberculin skin test reaction in millimeters, the relative risk of developing TB disease, and risk factors for drug side effects. Concurrent conditions that increase the risk of TB disease include in part: HIV infection, organ transplantation with immunosuppression, chronic steroid usage, injection drug use history, hematologic or reticuloendothelial neoplasms, chronic renal failure, diabetes mellitus (insulin dependent), gastrectomy and other specific conditions resulting in nutritional deficiencies, head and neck malignancies, and silicosis.

Treatment of LTBI should be considered when the following indications have been identified, no medical contraindications to treatment exist, and previous adequate treatment has not been provided:

- **Recent convertor status:** the inmate has a measured tuberculin skin test that has increased within the past 24 months by  $\geq 10$  millimeters. Since relevant medical conditions (such as HIV co-infection) may not be apparent at the time of skin testing, all inmates who have an increase in their skin test reading by 5 millimeters or more during routine screening should be referred to a clinician for further evaluation to determine if treatment of LTBI is medically indicated.

- **Inmates with HIV infection** or other immunocompromised conditions who are close contacts of an active TB case should be prescribed treatment for LTBI even if their tuberculin skin test measures 0 millimeters with or without evidence of anergy.

- Tuberculin skin test is **5 millimeters or greater** with the following concurrent conditions that increase the risk of tuberculosis disease:
  - Close contact to an active TB case
  - HIV co-infection, risk factors for HIV infection with unknown HIV serostatus, or other immunocompromised condition
  - Systemic corticosteroids, treatment for organ transplantation, or other immunosuppressive therapy (equivalent to 15 mg of prednisone or greater for 3 months or more of treatment)
  - Fibrotic changes on chest radiograph suggestive of inactive pulmonary TB (first evaluate sputum smears and cultures if fibrotic radiograph changes are possibly suggestive of active TB)
- Tuberculin skin test is **10 millimeters or greater regardless of age.**
- **Inmates in detention centers** should ordinarily not be prescribed LTBI treatment if their anticipated incarceration is uncertain or is less than several months unless the following high priority indications have been identified:
  - HIV co-infection or other immunocompromised condition
  - Close contact of an active TB case
  - Recent convertor status

#### **4. TREATMENT OF LTBI**

Multiple treatment regimens for LTBI have been recommended by the CDC as enumerated in Appendix 1, Treatment Regimens for Latent Tuberculosis Infection (LTBI). The antituberculosis medications used in these regimens differ in their dosages, potential toxicities, and monitoring requirements. The following general principles should be used when providing treatment for LTBI to inmates:

- Medication dosages for treatment of LTBI should be administered by direct observation.
- Completion of LTBI treatment should be determined by

counting doses of medication taken, not solely by duration of treatment, since missed doses may occur.

The following treatment regimens are recommended for LTBI:

**#1 - Isoniazid (INH), administered for 6 to 9 months,** is the preferred treatment regimen for LTBI and should be prescribed unless other medical or logistical reasons warrant an alternative regimen. Nine months of isoniazid should be administered when feasible and for all inmates with HIV co-infection. Isoniazid is prescribed as 15 mg/kg; (max: 900 mg) by mouth, twice weekly and administered by unit dose under direct observation (DOT) at least two days apart. Twice weekly isoniazid should be prescribed for 78 doses (approximately 9 months) for inmates with and without HIV co-infection; OR for 52 doses (approximately 6 months) for HIV seronegative inmates in which 9 months of therapy is not feasible. At the discretion of the treating physician, isoniazid may also be prescribed daily as 5 mg/kg; (max: 300 mg) by mouth, and administered by DOT for 270 doses (approximately 9 months) for inmates with and without HIV co-infection; OR daily for 180 doses (approximately 6 months) for HIV seronegative inmates in which 9 months of LTBI therapy is not feasible.

Pyridoxine should ordinarily be prescribed concurrently with isoniazid, usually as 50 mg daily by mouth, since pyridoxine helps prevent neuropathy and other isoniazid-related side effects in at-risk populations. Taking isoniazid along with phenytoin increases the serum concentrations of both drugs, consequently in inmates receiving both medications, the serum levels of phenytoin should be monitored closely and adjusted as necessary.

**#2 - Rifampin (RIF) 10 mg/kg (max: 600 mg) given daily, by mouth, plus pyrazinamide (PZA) 15-30 mg/kg (max: 2 gm) given daily, by mouth for 2 months** is an alternative treatment regimen for LTBI. Daily dosing of RIF + PZA should be prescribed for 60 doses (2-3 months) for inmates with HIV seronegative status and nonpregnant inmates in which INH for 6-9 months is not feasible. RIF + PZA is **not** recommended for pregnant women. Rifampin and pyrazinamide treatment for LTBI should be considered in the following clinical situations:

- Inmates who can not complete a 6-9 month treatment regimen of isoniazid for logistical reasons, but for whom TB prophylaxis is a high priority (e.g. HIV infection, close contact, or recent convertor)
- Inmates who can not tolerate isoniazid or have had an

adverse reaction

- Inmates with HIV infection who are not taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors (NNRTIs) and do not have other contraindications to rifampin or pyrazinamide, for whom a two month regimen is preferred for clinical or logistical reasons
- Inmates who are contacts of a case of active TB known to be INH-resistant and RIF sensitive

**Rifampin and pyrazinamide given twice weekly** has not been extensively evaluated, however, this regimen may be considered for selected inmates.

Rifampin has significant drug interactions with many medications and often reduces the effectiveness of other drugs. The prescribing clinician and pharmacy staff should review drug interactions carefully whenever prescribing rifampin.

**#3 - Rifampin (RIF) alone, 10 mg/kg (max: 600mg) given daily, by mouth for 120 doses (4 months)** is an alternative treatment regimen for LTBI. This regimen should be considered primarily for inmates with or without HIV infection who can not tolerate INH or PZA.

**MDR-TB:** The proven treatment options for LTBI are frequently ineffective for the management of MDR-TB contacts.

**Ethambutol (EMB) 15-25 mg/kg plus pyrazinamide (PZA) 15-30 mg/kg (max: 2 gm); OR a quinolone (i.e. levofloxacin or ofloxacin) plus PZA given daily for 6-12 months** are alternative regimens reserved for inmate contacts of MDR-TB cases sensitive to these agents, but resistant to isoniazid and rifampin. EMB + PZA should be prescribed daily for at least 180 doses for HIV seronegative inmates and up to 360 doses for HIV seropositive inmates. Consultation with a TB expert is recommended when treating contacts of persons with MDR-TB.

## **5. SPECIAL CONSIDERATIONS FOR TREATMENT OF LTBI**

**Contraindications** to treatment of LTBI: Treatment of LTBI should not be initiated if contraindications to treatment exist, including but not necessarily limited to the following:

- Radiologic or clinical evidence of active TB disease.
- Symptoms or signs of active hepatitis or other medical

conditions that would complicate treatment. Some experts recommend that isoniazid be withheld if a patient's transaminase level exceeds three times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is asymptomatic. Inmates who have significant elevations in liver transaminases should only be considered for treatment of LTBI if they are at high risk of developing active TB disease. Consultation with a physician with expertise in treating LTBI is recommended.

- History of adverse reactions to medications prescribed for LTBI.

**HIV co-infection:** Persons with HIV infection and LTBI are at significant risk of developing active TB disease and are therefore considered priority candidates for treatment. When prescribing isoniazid for treatment of LTBI, nine months of treatment is recommended. Rifampin and pyrazinamide for two to three months is an acceptable alternative treatment regimen for LTBI for inmates with HIV infection. **Rifampin, however, is contraindicated for patients with HIV co-infection who are taking protease inhibitors or NNRTIs.** Although data are limited, rifabutin (RFB) may be substituted for rifampin for treatment of LTBI when given in combination with indinavir, nelfinavir, amprenavir, ritonavir, and efavirenz, but not with hard-gel saquinavir, or delavirdine. Data regarding use of rifabutin with soft-gel saquinavir or nevirapine are limited. The recommended dosage of rifabutin will depend on the specific antiretroviral medication prescribed and should be determined in consultation with pharmacy staff. Dosage adjustments for antiretroviral medications may also be indicated when using rifabutin. Rifabutin is not recommended for persons taking multiple protease inhibitors or multiple NNRTIs since drug interactions are complex and poorly understood.

Inmates with HIV infection who are close contacts of a person with infectious TB disease should be considered for treatment of LTBI regardless of tuberculin skin test results.

**Pregnancy:** Pregnancy itself does not significantly influence the pathogenesis of TB or the risk of LTBI progressing to active TB disease. Therefore, treatment of LTBI with isoniazid is not routinely recommended during pregnancy. Daily or twice weekly isoniazid for 6-9 months should be prescribed 1-2 months following delivery in most cases. Pregnant women at high risk of developing TB disease (e.g. a positive tuberculin skin test who are close contacts of an active TB case, are recent convertors,

or have concurrent HIV infection or other immunosuppressive conditions) should be considered for isoniazid treatment of LTBI during pregnancy with close monitoring for hepatitis. No harmful effects on the fetus have been observed with isoniazid therapy.

**Old TB:** Inmates with abnormal chest radiographs suggestive of prior TB infection should be evaluated on a case by case basis in consultation with physicians experienced in diagnosing TB. Calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping usually represent primary healed TB rather than active TB disease. Treatment of LTBI in persons with evidence of primary healed TB depends on the patient's history, tuberculin skin test results, and risk factors for TB disease.

Persons with old fibrotic changes on chest radiograph suggestive of previous infection with TB, a positive tuberculin skin test of  $\geq 5$  millimeters, without evidence of active disease and no history of treatment for TB should be considered for treatment of LTBI. Sputum examination is usually warranted to rule out active TB disease prior to initiating treatment of LTBI in persons with fibrotic changes on chest radiograph. In some cases, clinicians may elect to initiate treatment for TB disease while awaiting sputum culture results for *M. tuberculosis*.

**BCG vaccination:** A history of BCG vaccination, with or without a BCG scar, should not influence treatment decisions for LTBI.

## **6. MONITORING AND DOCUMENTATION OF TREATMENT FOR LTBI**

Inmates considered for treatment of LTBI should be evaluated by health care staff in accordance with the following guidelines:

- A **baseline evaluation** should be conducted by a clinician as enumerated above with further review by a physician if treatment is indicated.

- **Counseling:** Inmates should be counseled by health care staff about the importance of adherence to every dose of treatment for LTBI. Pharmacy staff and other health care staff as appropriate should educate inmates about potential drug side effects, especially the signs and symptoms of hepatitis. Inmates should be warned that rifampin may give urine, saliva or tears an orange color and can stain contact lenses. Group counseling or other structured educational efforts should be considered for inmates who refuse treatment for LTBI when treatment is clearly indicated.

- **Medication administration** should be documented using the Federal Bureau of Prisons Tuberculosis Preventive Treatment Program Medication Administration Record (BP-634(60)).

- **Monitoring drug side effects:** The risk of hepatitis from isoniazid is low, but may be increased in older persons (>50 years of age), women, and during the third trimester of pregnancy and the postpartum period. All inmates should have baseline liver transaminases measured and should be subsequently monitored for signs and symptoms of hepatitis and other medication side effects. Inmates should be interviewed by a clinician, pharmacy or nursing staff for symptoms of anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, fatigue or weakness lasting three or more days, abdominal pain, easy bruising or bleeding, and arthralgias. Interviews should be conducted monthly if prescribed isoniazid or rifampin alone, and at two, four, and 8 weeks for inmates prescribed rifampin plus pyrazinamide for two months. Inmates who are nonadherent to treatment or who report symptoms suggestive of an adverse drug reaction or a serious drug side effect should immediately be referred to a clinician for further evaluation.

Evaluation of drug side effects for inmates receiving treatment for LTBI should be documented using the Federal Bureau of Prisons Side Effect Interview and Monitoring Form for LTBI, (English and Spanish, BP-s652.06X). The form requires the inmate's signature upon the initiation of treatment. Health care staff should read the form to illiterate inmates. The form should ordinarily be maintained by pharmacy staff, made available to clinicians for review, and a copy placed in the inmate's medical record at the completion or discontinuation of treatment.

- **Clinician follow-up care:** Routine follow-up clinician evaluations during treatment of LTBI should be scheduled on a case by case basis as determined by the responsible physician. Inmates with baseline elevations of liver transaminases or other complicating medical conditions should be followed closely.

- **Monitoring drug toxicities:** Monitoring liver transaminases is not routinely recommended during treatment of LTBI. However, liver transaminases, and liver function tests as necessary, should be monitored periodically for the following inmates:

- Inmates with significant elevations in baseline liver transaminases

- Inmates with chronic liver disease from alcohol, viral

hepatitis or other etiologies

- Inmates concurrently prescribed other potentially hepatotoxic drugs
- Inmates with a history of previous adverse reactions to the medications used in treating LTBI
- Pregnant women

Treatment for LTBI should ordinarily be discontinued if liver transaminases exceed three times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the inmate is asymptomatic.

The same guidelines for monitoring hepatotoxicity from isoniazid should be used for inmates taking rifampin and/or pyrazinamide. A complete blood count and platelet count should also be obtained prior to initiating rifampin therapy, and repeated as clinically indicated. Pyrazinamide may cause elevations in serum uric acid levels, however, asymptomatic hyperuricemia does not require treatment. Inmates with active gout should not be prescribed pyrazinamide, except in unusual circumstances when no other treatment options are available.

- **Chest radiographs**, other than baseline, are not indicated during treatment of LTBI, unless symptoms of TB disease develop during treatment.

**Treatment interruption or discontinuation:** Inmates failing to complete a treatment regimen for LTBI on two or more occasions should be evaluated on a case by case basis to determine if additional retreatment efforts are clinically prudent based on the inmate's risk factors for TB disease, previous cumulative doses of administered preventive therapy, and anticipated adherence to therapy. When reinstituting therapy for inmates who have stopped taking their medications for LTBI or have had therapy interrupted for medical reasons, clinicians may need to continue the regimen originally prescribed to complete the recommended duration of the particular regimen, or renew the entire regimen if interruptions were frequent or prolonged enough to preclude completion of treatment as originally prescribed. In either situation, **when therapy is reinstituted after an interruption of more than two months, a medical examination to rule out active TB is indicated.**

Inmates who decline treatment for LTBI, or have treatment

discontinued because of drug side effects, nonadherence, or other reasons, should be monitored in accordance with the following:

- Semiannual chest radiographs and clinician evaluations for symptoms and signs of pulmonary TB for inmates with HIV infection (or unknown HIV serostatus) or other immunosuppressive conditions.
- Semiannual chest radiographs and clinician evaluations for symptoms and signs of pulmonary TB for a two year period, for HIV seronegative inmates who are recent convertors or close contacts of active tuberculosis cases.

**Documentation of treatment regimen:** Treatment of LTBI should be documented by the responsible physician and other health care staff as appropriate using the Federal Bureau of Prisons Treatment Record for Latent Tuberculosis (BP-s636). The form should be maintained in the inmate's medical record and documentation updated:

- At the baseline evaluation and initiation of treatment
- Whenever treatment is interrupted or discontinued
- At the completion of treatment

Inmates who refuse treatment for LTBI should sign a refusal form in their medical record, documenting their declination of treatment.

## **7. DIAGNOSIS OF ACTIVE TUBERCULOSIS DISEASE**

The expedient diagnosis of active contagious TB is critical for providing effective treatment and for preventing the transmission of *M. tuberculosis* in the correctional setting. Inmates entering BOP facilities should be screened by symptom review, tuberculin skin testing, and chest radiographs in accordance with BOP policy so that TB disease is detected as soon as possible. Universal chest radiograph screening (rather than targeted screening) of all inmates entering the prison may be medically prudent for facilities managing inmate populations with a high incidence of TB disease.

**Diagnostic issues:** Although many inmates with active TB disease are symptomatic with positive tuberculin skin tests and characteristic abnormal chest radiographs (upper lobe/cavitary lesions) correctional health care providers should maintain a

high index of diagnostic suspicion for TB and be alerted to the following:

- An estimated 25% of patients with active TB disease will have negative (0 millimeter) tuberculin skin test measurements, particularly if immunocompromised.
- Inmates with active TB disease may be relatively healthy appearing and deny symptoms.
- Tuberculosis disease is associated with HIV infection, alcoholism, chronic renal failure, diabetes mellitus, neoplastic diseases, and drug abuse.
- Reactivation pulmonary TB commonly presents with cavitary upper lobe disease. Pulmonary TB, however, may exist even when the chest radiograph is completely normal or mildly abnormal, particularly with HIV co-infection. Other atypical presentations of active TB disease are common with advanced HIV infection, including lower lung zone infiltrates without cavities, and intrathoracic lymphadenopathy without pulmonary infiltrates.
- Extrapulmonary TB: TB can occur in nearly any organ of the body and should always be considered when an inmate presents with a fever or infection of unknown etiology that does not respond to routine antibiotic therapy. Extrapulmonary TB is usually more difficult to diagnose than pulmonary TB. Presentations may include in part: lymphadenitis (painless swelling of one or more lymph nodes), pleuritis, pericarditis, renal disease (mild dysuria/hematuria/flank pain/sterile pyuria), skeletal disease (arthritis/bone pain/bone deformities), meningitis, peritonitis, and epididymitis.

**Sputum collection:** Self-induced sputum specimens collected from TB suspects should be obtained in properly ventilated areas or in an NPIR by health care providers wearing adequate personal respiratory protection. Inmates should be instructed prior to coughing that nasopharyngeal discharge and saliva are not sputum; rather the specimen material sought is brought up from the lungs after a deep productive cough. A series of at least **three** specimens should be collected on separate days and transported to the laboratory as soon as possible. A State laboratory or other reliable TB laboratory recommended by the State Health Department should be utilized.

**Sputum induction:** Inhalation of an aerosol of sterile hypertonic saline (3-15%) produced by an ultrasonic nebulizer can be used to

induce sputum for inmates who have a nonproductive cough. **Sputum induction should be performed either in an NPIR or in a community-based medical facility** where adequate infection control measures can be ensured. If pulmonary TB disease is suspected, but sputum specimens can not be obtained, more invasive diagnostic procedures such as bronchoalveolar washes or transbronchial biopsies should be pursued.

**Smears and Cultures:** AFB smears can be processed and reported within hours of receiving a sputum specimen and thus provide a rapid diagnostic tool for detecting *M. tuberculosis*. An estimated 50%-80% of persons with pulmonary TB have positive sputum smears, however AFB smear positivity does not confirm the diagnosis of pulmonary TB. Furthermore, AFB smears are not specific for *M. tuberculosis*, since other nontuberculous mycobacteria are also AFB smear positive. Negative AFB smears do not necessarily preclude the presence of active TB disease.

All clinical specimens suspected of containing *M. tuberculosis* should be inoculated onto culture media. Culturing is more sensitive than microscopy (AFB smear positivity), allows for the precise identification of the mycobacterium species, and permits drug susceptibility testing and genotyping. Drug susceptibility testing should be performed on all positive cultures for *M. tuberculosis*. Genotyping is indicated for investigating possible TB outbreaks. The use of broth systems for culturing mycobacteria should be utilized whenever possible, since this method permits more rapid detection (1-3 weeks) of organisms than solid media (3-8 weeks).

Nucleic acid amplification can detect *M. tuberculosis* within hours and is useful for the rapid diagnosis of TB disease in certain clinical situations. Confirmatory bacterial cultures should also be obtained despite the results of nucleic acid amplification testing. Since the sensitivity and specificity of nucleic acid amplification varies based on several factors, clinicians should interpret results in consultation with experienced laboratory or health care professionals.

## **8. TREATMENT OF TB DISEASE**

All inmates with the clinical or laboratory diagnosis of TB disease should be considered candidates for four drug anti-tuberculosis initial drug therapy in accordance with the treatment guidelines enumerated in Appendix 2, Federal Bureau of Prisons Treatment Guidelines for Tuberculosis Disease, adapted from CDC recommendations.

The initial prescription of four drug antituberculosis therapy is essential for minimizing the development of further drug resistance, since inmates may have resistance to one or more TB drugs at baseline. Four drug therapy also hastens the conversion of AFB smears from positive to negative; thus reducing infectiousness. In certain cases in which MDR-TB is suspected, alternative treatments with four or more drugs may be indicated in consultation with a TB expert and the local or State health departments.

TB treatment regimens may require adjustments once drug susceptibility tests become available. Any deviations to the standard regimen are rarely indicated and should always be in accordance with the following caveats:

- **Never treat active TB with a single drug.**
- **Never add a single drug to a failing TB treatment regimen.**
- **Never switch to a two drug regimen of isoniazid and rifampin before drug sensitivities confirm non-resistant TB.**

All TB medications should be administered by directly observed therapy (DOT) to ensure adherence to the prescribed treatment regimen and reduce the emergence of resistant disease.

All TB medications should be prescribed according to the inmate's weight and adjusted appropriately with weight changes.

Clinical and/or radiographic improvement following empiric treatment for pulmonary TB with negative cultures is strongly suggestive of culture-negative pulmonary TB. Medications should be continued. If the clinical response to treatment is satisfactory, an abbreviated treatment course is usually indicated.

Extrapulmonary TB is generally treated using the same drug regimens as pulmonary TB, although TB osteomyelitis, lymphadenitis, and meningitis frequently require extended courses of treatment. Serial bacteriologic evaluations may be limited by disease location; therefore the response to treatment must be judged on the basis of clinical, and where applicable, radiologic findings.

**HIV co-infection:** TB disease complicated by HIV co-infection is treated with the same treatment regimens as TB without HIV infection for those inmates who are not receiving antiretroviral

drug therapy or are not prescribed protease inhibitors or NNRTIs. Rifampin is contraindicated in combination with protease inhibitors or NNRTIs, so an alternative non-standard TB treatment regimen should be prescribed rather than discontinuing effective antiretroviral therapy.

Rifabutin can be substituted for rifampin for treating TB for inmates prescribed indinavir, nelfinavir, amprenavir, ritonavir, and efavirenz, but not with hard gel saquinavir, or delvardine. Data regarding use of rifabutin with soft-gel saquinavir or nevirapine are limited. Rifabutin toxicity may result when prescribed with antiretroviral agents; monitor closely for arthralgias, symptoms of uveitis, leukopenia, and liver dysfunction. **Dosage adjustments of antiretroviral medications may be indicated when using rifabutin.** For inmates with contraindications to rifabutin, an alternative treatment option should be considered.

All inmates with active TB and HIV co-infection should be treated and monitored in consultation with an expert in treating HIV infection and TB, using current CDC guidelines. Although persons with TB and HIV infection usually respond adequately to anti-tuberculosis therapy, drug side effects are more frequent and bacteriologic response may be less sustained, necessitating careful monitoring and if necessary, an extended treatment course.

**Immune reconstitution:** TB disease and its associated systemic symptoms may be paradoxically exacerbated when persons with HIV co-infection are simultaneously treated with highly effective antiretroviral regimens, resulting in immune reconstitution with increased T-lymphocytes and enhanced cytotoxic activity against *M. tuberculosis*. Changes in antituberculosis or antiretroviral therapy are rarely necessary in persons with paradoxical reactions.

A physician consultant with TB treatment expertise and the local or State health department should be consulted for any of the following TB cases:

- A treated case of TB that does not result in negative cultures following two months of therapy.
- All cases of drug intolerance, pregnancy, or other situations requiring deviation from a standard treatment regimen.

- All cases of multi-drug resistance.

## 9. MONITORING TREATMENT OF TB DISEASE

All inmates with active TB disease should be monitored at least monthly by a physician to evaluate the clinical response to therapy and monitor side effects to medications. Baseline laboratory studies, TB medication regimens, and monitoring of adverse reactions should be in accordance with the parameters outlined in Appendix 2 and the following guidelines:

- Inmates with sputum cultures positive for *M. tuberculosis* should have three (3) adequate morning sputum cultures **obtained monthly until sputum cultures convert to negative**. Inmates who can not voluntarily provide a sputum sample at a BOP facility should have sputum induction performed in a negative pressure isolation room (NPIR) or should be sent to an appropriate community health care facility. **A final sputum culture should be obtained at the completion of successful treatment as a reference culture.**

**Sputum cultures positive for *M. tuberculosis* after two months of drug treatment are suggestive of ineffective therapy.** Repeat drug sensitivities should be obtained to evaluate for resistant disease. Inmates with TB disease who do not respond to standard drug therapy by two months of treatment may be nonadherent to their medication regimen or may have malabsorption, drug interactions, or other problems resulting in subtherapeutic serum drug levels. Persons with chronic gastrointestinal disease (e.g. Crohn's disease or HIV-related diarrhea) are particularly at risk for drug treatment failure. Serum drug levels should be obtained to document the adequacy of medication delivery for inmates with known malabsorption or who fail to respond to TB treatment.

Liver transaminases should be obtained at baseline. If baseline liver transaminases are elevated, liver function studies should be measured and screening conducted for HBV and HCV infections. Inmates with elevations in liver transaminases greater than 3-5 times normal are at higher risk for hepatotoxicity from isoniazid and other potentially hepatotoxic TB medications. Elevations in liver transaminases are not necessarily a contraindication to treatment, but consultation with a TB expert is recommended in determining the appropriate regimen for treatment of TB disease. Monthly monitoring of liver enzymes should be considered for the following conditions:

- Inmates with baseline liver transaminases greater than the

upper limit of normal

- Inmates with chronic liver disease from alcohol, viral hepatitis or other etiologies
- Inmates prescribed other potentially hepatotoxic drugs
- Pregnant women

Visual acuity and red-green color vision should be assessed at baseline and monthly thereafter for inmates treated with ethambutol. Optometry or ophthalmology evaluations are indicated at three months of treatment and every three months thereafter while inmates are receiving ethambutol.

Baseline and monthly creatinine and audiograms are indicated for inmates receiving streptomycin or other aminoglycosides.

Chest radiographs should be obtained at baseline, at the completion of therapy, and during treatment when clinically indicated.

## **10. CONTACT INVESTIGATIONS**

All TB cases should be investigated to assess the contagiousness of the index case and to determine if inmate, staff, or other contacts should be evaluated and/or notified. Extrapulmonary and pleural TB cases usually do not require a contact investigation. Contact investigations should be conducted in consultation with the local health department and Regional and Central Office administrative staff in accordance with the following guidelines:

- Contact investigations should be initiated by evaluating the closest inmate and staff contacts of the index case. In addition to this, the CDC recommends that an initial interview of the index case be initiated within three days after reporting the case to the local health department to determine more specific information about the symptoms, common places of daily activity, and to identify direct contacts to the index case (such as contact inmates that may not be included merely within the housing unit).
- All inmate contacts should have a medical record review and personal interview for symptoms of active TB. Symptomatic inmates should receive a chest radiograph and complete medical evaluation by a physician regardless of tuberculin skin test status and should be isolated in a negative pressure isolation

room (NPIR) if contagious TB is suspected by chest radiograph or clinical findings. All other asymptomatic inmate contacts do not require isolation.

- Mandatory tuberculin skin testing of all previously PPD-negative inmate contacts should be conducted at baseline (unless previously tested within 1-3 months of exposure) and repeated 10-12 weeks from the last contact with the source case. Contacts with tuberculin skin test readings of 5 millimeters or greater should be prescribed treatment for LTBI unless medically contraindicated.
- Immunocompetent inmate contacts with past histories of positive tuberculin skin tests should not be skin-tested, but should be interviewed for symptoms of active TB and should receive a chest radiograph if symptomatic.
- Inmate contacts with HIV infection or other serious immunocompromised conditions should receive chest radiographs regardless of skin-test status. Very close immunocompromised contacts, such as cell mates, should be prescribed treatment of LTBI regardless of tuberculin skin test results.
- If inmate contacts refuse medically indicated isoniazid prophylaxis they should be monitored by chest radiographs every six months for two years if HIV seronegative; and every six months indefinitely if HIV seropositive.
- All staff contacts should be evaluated for TB infection and TB disease in accordance with BOP policy.

If the initial contact investigation indicates that significant transmission of TB infection has occurred to other inmates or correctional staff, the contact investigation should be expanded to include evaluation of contacts who had less immediate contact with the index case. This investigation should be guided by State or local health department investigators using the "concentric circle": model.

## **11. INFECTION CONTROL MEASURES**

**Transmission:** Transmission of *M. tuberculosis* ordinarily occurs when bacteria are expelled into the air from a person infected with active, symptomatic pulmonary or laryngeal TB disease. Transmission of *M. tuberculosis* from one person to another depends on the length of time and frequency of the exposure, the degree of contagiousness of the infected person, the environment

and airflow in which the exposure occurred, and the intensity of the contact with the tuberculosis organism itself. Extrapulmonary and pleural TB are ordinarily not contagious unless infectious body fluids or drainage are aerosolized.

All inmates should be counseled during orientation to the institution and when appropriate during clinical evaluation of the importance of baseline and annual skin-testing for TB infection and symptom screening to detect potentially contagious TB disease. Inmates should be advised to seek medical attention whenever symptoms of TB disease occur. Inmates should be counseled that certain risks and conditions such as HIV infection, diabetes, chronic renal failure, injection drug use history, and close contact with someone who is sick with infectious TB, all pose a greater risk of getting TB disease.

**Containment:** Inmates with suspected or confirmed active TB disease should be managed while incarcerated in accordance with BOP policy and the following clinical guidelines:

- Inmates with contagious TB disease should be assigned to an NPIR until no longer infectious. Containment is ordinarily maintained until all of the following parameters are achieved:
  - Treatment with a four drug regimen per treatment guidelines or other equally effective regimen has been administered for at least two weeks by DOT.
  - The inmate shows clinical evidence of improvement.
  - Three consecutive, daily sputum smears are negative.
  - If drug resistance is suspected, drug sensitivities are documented and treatment is appropriate with clinical evidence of improvement (may take several weeks to report drug sensitivities).
- If AFB smears are negative, but TB is suspected based on the clinical presentation and chest radiograph findings, the inmate should be housed in an NPIR during initial diagnosis and treatment and not released until clinically improving and considered no longer contagious by the treating physician. TB treatment should be continued until sputum or bronchial washing culture results are available, at which time the need for further treatment should be reassessed.
- Inmates should be instructed to cover their mouth when they

cough or sneeze. Inmates may be instructed to wear a surgical mask during necessary transport such as for medical procedures. Movement of the inmate should be limited to those situations where movement is required for medical or security reasons.

- Inmates should be managed in an NPIR in accordance with BOP policy and current CDC recommendations on ventilation and air change rates per hour for TB isolation. The CDC recommends that verification of negative pressure of the NPIR is checked and recorded **daily** while isolation of a suspected or confirmed TB case is in effect. **Monthly** verification of negative pressure should occur at all other times.

- Traffic control and measures to contain airflow within the NPIR such as keeping all doors closed except for entering and exiting, should be maintained. Routine, standard decontamination procedures for non-disposable patient care items and environmental surfaces that may be moistened with secretions are sufficient upon discharge/release of the inmate from the NPIR. Routine, standard cleaning procedures are sufficient to control the spread of *M. tuberculosis* which is transmitted through the air rather than by fomites or direct contact. Cleaning should be in accordance with CDC guidelines on Handwashing and Hospital Environmental Control.

- Inmates should be managed using airborne precautions and personal respiratory protection designated to prevent the transmission of *M. tuberculosis*. All persons who come in close contact with contagious inmates should wear appropriate respiratory protection, in accordance with BOP policy and OSHA recommendations on respiratory protection. The minimal acceptable form of respiratory protection to protect against transmission of *M. tuberculosis* is the N-95 respirator.

- Appropriate engineering controls should be used upon discontinuation of TB isolation. The NPIR should be appropriately purged of airborne contaminants before the room is used to house another inmate or is occupied without the use of protective respiratory protection. Clearance times should be based on CDC guidelines on "Air changes per hour and time in minutes required for removal efficiencies of airborne contaminants," *MMWR*, Vol. 43, RR-13, table S3-1, page 72, (i.e. if an institution NPIR has been determined to provide 12 air changes per hour, it will take approximately 35 minutes to remove air contaminants to achieve the best removal efficiency rate of 99.9% and prevent transmission to others).

## **12. DISCHARGE PLANNING**

Inmates receiving treatment for LTBI or TB disease should have their treatment plan coordinated with community providers by the time of release to help ensure continuity of care and maintain public health. All inmates with active TB disease should have a specific plan for continuing treatment with the receiving State health department and local community public health providers. Specific referrals for community-based treatment of LTBI should be coordinated and secured when feasible. The treating physician and other health care providers can improve continuity of care for inmates upon release by initiating the following:

- Coordinating release planning with case managers and community corrections staff in accordance with BOP policy.
- Providing counseling to ensure the inmate understands importance of adherence to treatment and specific instructions for seeking care upon release.
- Securing consent for release of medical information in accordance with BOP policy.
- Supplying TB medications in accordance with BOP policy.

## **ATTACHMENTS**

- Appendix 1: Treatment Regimens for Latent Tuberculosis Infection (LTBI)
- Appendix 2: Treatment Guidelines for Tuberculosis Disease
- Appendix 3: Clinician Self-Assessment: Medical Management of Latent Tuberculosis Infection and Tuberculosis Disease

## Federal Bureau of Prisons Treatment Regimens for Latent Tuberculosis Infection (LTBI)

Treatment of LTBI (Comments)	Treatment Regimens	Dosages		Administration	Side Effects	Monitoring Parameters
		DAILY DOSE (MAXIMUM)	TWICE WEEKLY DOSE (MAXIMUM)			
<p>LTBI treatment should not be initiated until active TB disease has been eliminated as a potential diagnosis.</p> <p>Also, refer to clinical guidelines on “<i>Indications for LTBI treatment</i>” and “<i>Special considerations related to HIV co-infection, pregnancy, old TB.</i>”</p> <p>Consultation with a TB expert is recommended when treating contacts of persons with MDR-TB. An alternative regimen is indicated.</p>	<p><b>#1:</b> <b>INH</b>, 6 to 9 months</p> <p>(9 mo is preferred regimen)</p>	<p><b>#1: INH 5 mg/kg</b> (300 mg/day)</p> <p>Daily dose x 180 doses (within 6 mo) to 270 doses (within 9 mo)</p> <p>Note: give pyridoxine (vitamin B<sub>6</sub>) 50 mg/day concurrently with INH.</p>	<p><b>#1: INH 15 mg/kg</b> (900 mg/dose)</p> <p>Twice weekly x 52 doses (6 mo) or 78 doses (9 mo)</p> <p>Note: administer twice weekly, at least two days between doses.</p>	<p>#1: Offer 6 mo if 9 mo Tx not feasible. If 6 mo not feasible, consider alternative regimen.</p> <p>Always give 9 mo regimen for HIV+</p> <p>B<sub>6</sub> 50 mg/day to prevent INH-associated peripheral neuropathy.</p>	<p>-anorexia -nausea, vomiting -dark urine -icterus, rash -paresthesias of hands and/or feet -fatigue or weakness lasting &gt; 3 days -abdominal pain -easy bruising or bleeding -arthralgias.</p>	<p>Baseline CXR to rule out active TB (if suggestive of old healed TB, should have 3 consecutive sputum samples to rule out active TB disease). If sputum-negative, further diagnostic evaluation should be pursued.</p> <p>Conduct clinical evaluation. Obtain baseline hepatic enzymes (ALT and AST) and HIV test if not previously done. Bilirubin/LFTs if hepatic enzymes are elevated.</p>
	<p><b>#2:</b> <b>RIF/PZA</b>, 2 months</p> <p><b>Many drug interactions with RIF: review drug regimen carefully</b></p>	<p><b>#2: † RIF 10 mg/kg (600 mg/day) and PZA 15 - 30 mg/kg (2g/day)</b></p> <p>Daily dose X 60 doses within 2- 3 mos.</p> <p>† RFB may be substituted for RIF when given with certain PIs+NNRTIs (consult pharmacist for drug dosages)</p>	<p><b>#2: RIF 10 mg/kg (600 mg) and PZA 50-70 mg/kg (4 g/day)</b></p> <p>Consider this regimen only for select inmates if alternative regimens are not feasible. Note: RIF twice weekly dosage the same as daily dosage.</p> <p>Regimen should consist of at least 16-24 doses within 2-3 mo</p>	<p>#2: Consider RIF+PZA if:</p> <p>-INH is not tolerated.</p> <p>-A close contact of an active TB case with INH-resistance and RIF-sensitivity.</p> <p>-HIV+ on ART: RIF given <u>without</u> concurrent protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)/See RFB note</p>	<p>RIF/ RFB colors body fluids orange; stains contact lenses.</p> <p>Risk of leukopenia and low platelets with RFB.</p> <p>PZA is not recommended if chronic gout exists.</p>	<p>Monitoring ALT/AST is not routinely necessary during LTBI Tx, but is indicated periodically if:</p> <p>-baseline LFTs were sig. † -chronic liver disease -pregnancy -taking other hepatotoxic drugs</p> <p><u>Other lab:</u> CBC, platelets, if on RIF or RFB; uric acid if on PZA Other labs at physician discretion</p>
	<p><b>#3: RIF</b> 4 months</p>	<p><b>#3: RIF 10 mg/kg (600 mg/day)</b></p> <p>Daily dose X 120 doses within 4 - 6 months.</p>	<p><b>#3: RIF ALONE TWICE WEEKLY IS NOT RECOMMENDED</b></p>	<p>#3: Indicated primarily if inmate is intolerant to INH and/or PZA.</p>	<p>Same as #2</p>	<p>Monitor for drug side effects at 2, 4, and 8 weeks if receiving RIF + PZA; and monthly if receiving INH or RIF monotherapy.</p>

INH-isoniazid; RIF-rifampin; PZA-pyrazinamide; RFB-rifabutin; ART-antiretroviral therapy. Adjust dosages as weight changes. Doses must be given by directly observed therapy (DOT).

# FEDERAL BUREAU OF PRISONS TUBERCULOSIS TREATMENT GUIDELINES

Diagnostic Category	Length of Regimen	Initial Phase INH/RIF/PZA/EMB (or SM) for 8 weeks (daily for 2 weeks, then biweekly for 6 weeks)		CONTINUATION PHASE INH/RIF for 16 weeks (2 OPTIONS)		MONITORING PARAMETERS
Adults - TB  Culture positive - pulmonary or extrapulmonary	6 months minimum  Longer treatment may be required for TB meningitis or bone/joint TB	<b>DAILY DOSE (MAXIMUM DOSE)</b> Daily dose x 14 doses  INH 5 mg/kg (300 mg/day)  RIF 10 mg/kg (600 mg/day)  PZA 15-30 mg/kg (2g/day)  EMB 15-25 mg/kg  or  SM 15 mg/kg ≤60 yr. (1.0 g/day)  SM 10 mg/kg if >60 yr. Old (750 mg - 1 g)  Note: EMB should be started at 15 mg/kg to reduce the risk of ocular toxicity. The use of 25 mg/kg should be reserved for patients requiring retreatment, or treatment of drug resistant TB.	<b>TWICE WEEKLY DOSE (MAXIMUM DOSE)</b> Twice weekly x 6 weeks.  INH 15 mg/kg (900 mg/dose)  RIF 10 mg/kg (600 mg/dose)  PZA 50-70 mg/kg (4g/dose)  EMB 50 mg/kg/dose  or  SM 25-30 mg/kg ≤60 yr. (1.5 g/dose)  SM 750 mg - 1 gram if >60 yrs)  Note: Pyridoxine - 50 mg/day should be given concurrently with INH to prevent INH-associated peripheral neuropathy.  Drugs prescribed twice weekly should be administered 2 or 3 days apart.	<b>DAILY DOSE (MAXIMUM DOSE)</b>  INH 5 mg/kg (300 mg/day)  RIF 10 mg/kg (600 mg/day)   Note: AFTER 8 WEEKS OF 4 DRUG THERAPY NEVER SWITCH TO 2 DRUGS UNTIL SUSCEPTIBILITY TO INH AND RIF IS DEMONSTRATED.	<b>TWICE WEEKLY DOSE (MAXIMUM DOSE)</b>  INH 15 mg/kg (900 mg/dose)  RIF 10 mg/kg (600 mg/dose)   Note: Drugs prescribed twice weekly should be administered 2 or 3 days apart.	<b>Baseline:</b> Chest x-ray, morning sputums for AFB X 3, CBC, platelet count, creatinine, uric acid, bilirubin, hepatic enzymes, visual acuity/red-green color perception(EMB), and audiogram(SM).  <b>Do</b> susceptibility drug testing with first sputum cultures and as needed.  <b>Ongoing:</b> Monthly evaluation by a physician for symptoms and targeted exam  ALT/AST monthly if elevated at baseline Creatinine/audiogram monthly on SM  Visual acuity/red-green color vision monthly, eye doctor evaluation every 3 months while on EMB  Certain high-risk groups, may have increased propensity for INH-induced hepatitis and require monthly liver enzymes. Presence of hepatitis does not preclude treatment for TB—patient must be monitored closely. Other labs at discretion of physician.  Obtain 3 consecutive daily sputums for smear and culture every month until conversion. Repeat drug susceptibility testing if patient fails to respond clinically or remains culture positive after 2 months. Chest x-ray, sputum smear and culture at end of treatment for future comparisons.
Adults -  Pulmonary with negative smear and culture. Patient is symptomatic.	4 months minimum  6 months if HIV infected.	<b>INITIAL PHASE</b> INH/RIF/PZA/EMB (or SM) for 8 weeks		<b>CONTINUATION PHASE</b> INH/RIF for 8 weeks		Same as above  Chest x-ray at 3 months. Failure of x-ray to respond to treatment within 3 months suggestive of previous (not current) TB or another disease.

Diagnostic Category	Length of Regimen	Initial Phase INH/RIF/PZA/EMB (or SM) for 8 weeks (daily for 2 weeks, then biweekly for 6 weeks)		CONTINUATION PHASE INH/RIF for 16 weeks (2 OPTIONS)		MONITORING PARAMETERS
		Same as above	Same as above	Doses same as above. Continue EMB and PZA if drug resistance likely.	Doses same as above. Continue EMB and PZA if drug resistance likely.	

INH-isoniazid, RIF-rifampin, PZA-pyrazinamide, EMB-ethambutol, SM-streptomycin. Adjust dosages as weight changes. Medicines must be given by directly observed therapy (DOT).

Appendix 2, page 2

### FEDERAL BUREAU OF PRISONS TUBERCULOSIS TREATMENT GUIDELINES - SPECIAL CONSIDERATIONS

DIAGNOSTIC CATEGORY	REGIMEN	MEDICATIONS	MONITORING PARAMETERS
Pregnancy	9 months minimum. Treatment should begin as soon as TB is suspected.	<p>Treat with appropriate doses of INH/RIF/EMB. Do not use PZA unless dealing with drug-resistant disease with no alternatives. Inadequate tetratogenicity data for PZA</p> <p>Give Pyridoxine (B6) 50 mg/day concurrently.</p> <p>SM has documented harmful effects on the fetus and should not be used.</p> <p>Discontinue EMB once INH/RIF sensitivity results are documented.</p> <p>Consult with physician expert for appropriate treatment regimen</p>	<p>Baseline: Chest x-ray, morning sputums for AFBX 3, CBC, platelet count, serum creatinine, uric acid, liver enzymes, visual acuity, and red-green color vision.</p> <p>Ongoing: Monthly symptom review and exam by clinician. Assess visual acuity/ red-green color perception monthly and eye doctor evaluation every 3 months while on EMB. With hepatic disease, renal disease or gout obtain monthly liver function tests, creatinine, or uric acid respectively. Certain high-risk groups for isoniazid-induced hepatitis require monthly liver enzymes. Presence of hepatitis does not preclude treatment for TB. Patient must be monitored closely. Other laboratory studies at the discretion of the physician.</p> <p>Obtain 3 consecutive daily sputums every month until conversion. Do susceptibility drug testing with first cultures and as needed. Repeat drug susceptibilities if patient fails to respond clinically or remains culture positive after 2 months.</p> <p>Chest x-ray, sputum smear and culture at end of treatment and more frequently as indicated. If pregnant woman is HIV positive or has drug resistant TB, consult infectious disease consultant.</p>
HIV Infection	Standard 6 month regimen, unless patient on certain antiretroviral drugs - then consult CDC guidelines and TB expert for treatment recommendations	Treatment may need to be prolonged due to adverse drug reactions or poor drug absorption. RIF contraindicated with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. RFB can be substituted for RIF with certain antiretroviral drugs (consult pharmacist)	Adverse reactions more common. Monitoring same as for adult standard. If rifabutin prescribed, monitor for uveitis, arthralgia, and leukopenia. If there is no culture conversion at the end of 2 months, reevaluate patient and repeat drug susceptibility tests. Treatment should be prolonged with any evidence of suboptimal response with therapy.
INH Resistance/ Intolerance	6 months of 4-drug standard regimen effective. After INH resistance/intolerance identified, discontinue INH. Tx with RIF/ PZA/EMB for duration of therapy given twice weekly.	Same as adult standard excluding INH from regimen.	Same as adult standard. Monitor cultures and drug sensitivities closely.

INH/Rifampin resistance (MDR-TB)	Continue treatment until bacteriologic sputum conversion followed by 12-24 months of at least 3 drug treatment.	Give at least three new drugs to which the organism is susceptible.  Consult with tuberculosis expert to ensure effective medical management.	Same as adult and children standards with monthly monitoring of cultures and drug sensitivities until conversion.
----------------------------------	-----------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------

INH-isoniazid, RIF-rifampin, PZA-pyrazinamide, EMB-ethambutol, SM-streptomycin, RFB-rifabutin. Adjust dosages as weight changes/ Administer all drugs by DOT.

## **Clinician Self-Assessment: Medical Management of Latent Tuberculosis Infection and Tuberculosis Disease**

### **Question #1**

Which of the following statements regarding the diagnosis of latent tuberculosis infection (LTBI) is false?

- A. Inmates with a history of BCG vaccination should be screened with tuberculin skin testing.
- B. Tuberculin skin test results are read by measuring induration, not erythema.
- C. Filling tuberculin syringes several hours before administering a tuberculin skin test can affect the result.
- D. Anergy testing is routinely warranted in inmates with HIV infection.
- E. Pregnancy is not a contraindication to tuberculin skin testing.

### **Question #2**

Which of the following is false regarding interpretation of tuberculin skin test results?

- A. A 5 millimeter PPD is considered positive for an inmate with HIV infection.
- B. A 5 millimeter PPD is considered positive for an inmate who is a recent contact of an active TB case.
- C. A 10 millimeter PPD is considered positive for all inmates regardless of age.
- D. A recent convertor is a person that has had a tuberculin skin test increase by at least 5 millimeters within the past two years.
- E. A 5 millimeter PPD is considered positive for inmates with fibrotic changes on chest radiograph suggestive of old TB infection.

### **Question #3**

Which of the following inmates is not a candidate for treatment of LTBI?

- A. A 40 year old inmate from China with a PPD of 7 millimeters.
- B. An HIV seropositive inmate with a PPD of 7 millimeters.
- C. A 55 year old inmate with a PPD of 10 millimeters
- D. A 40 year old asthmatic on 20 mg of prednisone for 6 months with a PPD of 5 millimeters.
- E. An inmate with AIDS with a 0 millimeter PPD whose cell mate was just diagnosed with contagious TB disease.

**Question #4**

Which treatment is not recommended for LTBI?

- A. Isoniazid for 9 months
- B. Isoniazid for 6 months
- C. Rifampin for 4 months
- D. Rifampin/Pyrazinamide for 2 months
- E. Ethambutol for 9 months

**Question #5**

Which of the following is false regarding potential drug toxicities and interactions?

- A. Ethambutol can cause optic neuritis.
- B. Isoniazid can cause hepatotoxicity.
- C. Rifampin can turn body fluids orange.
- D. Pyrazinamide frequently causes gout
- E. Rifampin is not recommended with protease inhibitors.

**Question #6**

Which of the following is false regarding TB disease?

- A. TB disease can occur in a person with a negative PPD.
- B. A positive AFB sputum smear is diagnostic of pulmonary TB.
- C. A person with HIV infection and pulmonary TB may have a normal chest radiograph.
- D. Extrapulmonary TB may present as fever of unknown origin.
- E. A person can have pulmonary TB with negative AFB smears.

**Question #7**

Which of the following is false regarding the treatment of TB?

- A. All medications should be given by direct observation.
- B. Persons with TB disease who respond to treatment usually require 6 months of medications.
- C. Isoniazid/rifampin is recommended for initial treatment of TB disease in federal inmates.
- D. Partial adherence to treatment may result in multi-drug resistant TB disease.
- E. Drug sensitivities should always be obtained.

**Question #8**

Which of the following should most concern you when managing a patient with pulmonary TB disease?

- A. The inmate develops hyperuricemia.
- B. Sputum cultures remain positive after 3 months of treatment.
- C. Chest x-ray findings from TB disease do not change significantly after two weeks of treatment.
- D. Drug sensitivities indicate resistance to isoniazid.
- E. AFB smears are still positive after 3 weeks of drug therapy.

**Question #9**

INH prophylaxis for LTBI should be discontinued due to which of the following findings?

- A. Elevated uric acid levels.
- B. ALT exceeds three times normal in an asymptomatic inmate.
- C. Mild paresthesias of the hands and/or feet.
- D. ALT exceeds five times normal in an asymptomatic inmate.
- E. Inmate reports urine is orange.

**Question #10**

True or False: Liver transaminases (ALT and AST) should be monitored monthly in all inmates taking INH.

## **Answers to Self-Assessment Quiz**

### **Question #1 - Answer is D**

Anergy testing is not indicated as a component of tuberculin skin testing for any inmates, including those with HIV infection. Anergy panel antigens are poorly standardized and do not predict an adequate response to PPD testing. The tuberculin skin test is quantified by measuring the largest diameter of indurated area (palpable swelling) on the forearm in millimeters. Erythema without induration does not indicate reactivity to tuberculin testing. BCG vaccinations are poorly standardized and have unproven efficacy for preventing TB disease. Persons with a history of BCG vaccination should receive tuberculin skin testing unless they have a history of a previous positive reaction to tuberculin skin testing. Tuberculin skin tests can be administered safely to pregnant women. The tuberculin purified protein derivative (PPD) when diluted in a buffered diluent is adsorbed in varying amounts by glass and plastics. To minimize reduction in potency by adsorption, tuberculin should never be transferred from one container to another, and skin tests should be given as soon after the syringe has been filled as possible.

### **Question #2 - Answer is D**

A recent convertor is defined as an individual who has a negative tuberculin skin-test reaction that increases in reaction size by  $\geq 10$  millimeters within a period of two years, suggestive of recent infection with *M. tuberculosis*. Recent convertors have a relative increased risk of developing active TB disease and therefore are priority candidates for treatment of LTBI.

### **Question #3 - Answer is A**

Treatment of LTBI is recommended for all inmates with tuberculin skin tests of 10 millimeters of induration or greater, unless contraindications exist. Immunosuppressed inmates, persons with evidence of inactive TB (characteristic fibrotic changes on chest radiograph) or close contacts of a person with contagious TB disease are candidates for treatment of LTBI if their tuberculin skin test is 5 millimeters or greater. Inmates with AIDS who are close contacts of a person with contagious TB disease are candidates for treatment of LTBI regardless of tuberculin skin test results.

### **Question #4 - Answer is E**

The CDC has expanded recommended treatment options for LTBI. Nine months of isoniazid is the preferred regimen for both HIV seronegative and HIV seropositive federal inmates, however, other regimens may be considered based on the inmate's risk factors for TB disease, exposure history, potential adverse drug reactions, adherence concerns, concurrent medication usage, and anticipated duration of incarceration. Monotherapy with ethambutol is not a

proven treatment option for LTBI.

**Question #5 - Answer is D**

Pyrazinamide can cause hyperuricemia, but gout does not ordinarily develop despite elevated levels of uric acid. Individuals with a history of gout may, however, experience an exacerbation if given PZA. Rifampin is usually contraindicated with protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Rifabutin can be substituted for rifampin with certain antiretroviral regimens.

**Question #6 - Answer is B**

Positive AFB smears of sputum, although suggestive, are not diagnostic of *M. tuberculosis* organisms, since other nontuberculous mycobacterial species are also AFB positive. Extrapulmonary TB can be a cryptic disease and present with chronic fever as the only symptom. Persons with HIV co-infection and TB disease may have atypical presentations of TB, including normal chest radiographs. Although persons with pulmonary TB often have positive AFB smears, TB disease may be present with positive sputum cultures without detectable organisms on AFB smears of sputum.

**Question #7 - Answer is C**

All inmates with TB disease should be treated with anti-tuberculosis medications in accordance with CDC guidelines. Four drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol is ordinarily recommended as initial therapy given for two months followed by four months of isoniazid and rifampin. An alternative treatment regimen may be indicated in certain situations such as potential drug interactions or drug resistance. Initial two drug therapy is not recommended in part because of the possibility of drug resistance. A single drug should NEVER be added to a failing TB drug regimen. All medication doses should be given under direct observation. Lack of adherence to drug therapy can result in drug resistance and treatment failure. Drug sensitivities should be obtained from positive cultures to ensure that appropriate medications are prescribed.

**Question #8 - Answer is B**

Sputum cultures should convert to negative after two months of effective therapy. Persistently positive cultures suggests nonadherence to therapy, drug resistance, malabsorption of medications, or other potentially serious problem. Chest radiographs would not be expected to show signs of improvement after only two weeks of effective therapy for pulmonary TB. AFB smears may remain positive even with effective therapy and usually represent dead organisms in this setting. Hyperuricemia often develops with pyrazinamide but is generally well tolerated

without gouty arthritis or other complications. Isoniazid-resistant TB can be effectively treated with three drug therapy with rifampin, pyrazinamide, and ethambutol.

**Question #9 - Answer is D**

INH should be discontinued in an asymptomatic inmate if ALT or AST exceeds five times the upper limit of normal. If symptoms such as fatigue, anorexia, or nausea are present, INH should be discontinued if the ALT or AST exceeds three times normal and the inmate should be followed closely for worsening hepatitis. Mild paresthesias do not necessitate discontinuation of INH, and may resolve spontaneously or with administration of pyridoxine. Uric acid levels are unaffected by INH, but may rise with PZA administration. Orange urine is characteristic of rifampin and rifabutin, whereas dark urine may reflect hyperbilirubinemia from INH.

**Question #10 - Answer is False**

Routine (monthly) monitoring of liver transaminases is not indicated in all inmates. Periodic monitoring is recommended if the baseline ALT or AST is significantly elevated, if the inmate has known chronic liver disease of any etiology, if the inmate is taking other potentially hepatotoxic drugs which cannot be discontinued (e.g. methotrexate), or in pregnancy.